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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/429,003	10/29/99	SHARMA	P Q-56359

EXAMINER

HM22/0213

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EINSMANN, J

ART UNIT	PAPER NUMBER
1655	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/429,003	SHARMA ET AL.	
	Examiner	Art Unit	
	Juliet C. Einsmann	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. This action is written in response applicant's correspondence submitted 10/20/00, paper number 12. Claims18, 29, 31, 32, 33, 34, and 35 have been amended. Claims 18-35 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

2. This application is in compliance with the sequence rules.

Claim Rejections - 35 USC § 103

3. Claims 18-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wadhwa *et al.* (Molecular Biotechnology, Vol. 6, 1996, p. 213-217) in view of Ditkoff *et al.* (Surgery, 120(6): 959-964, 1996).

Wadhwa *et al.* teach a method of obtaining isolated selected cDNA species which comprising:

(a) isolating mRNA from a normal mouse cell line, reverse transcribing the mRNA, amplifying the cDNA, and labeling the resulting cDNA with denaturing loading dye (p. 214);

(b) isolating mRNA from a transformed clone, reverse transcribing the mRNA, amplifying the cDNA, and labeling the resulting cDNA with denaturing loading dye (p. 214);

(c) separating the cDNA species using gel electrophoresis (p. 214)

(d) selecting two or more cDNA species from the separated cDNA species obtained in step (c), which are present at a different level in the normal sample than in the diseased sample (Fig. 1)

(e) isolating and amplifying the resulting selected cDNA species (p. 215); and

(f) immobilizing the resulting isolated selected cDNA species on a Hybond N^+ membrane filter (p. 215).

Wadhwa *et al.* further teach that 16 primer pairs were used to amplify the cDNA's, and that for each of these primer pairs 3-5 differentially expressed bands were seen in either of the two samples (p. 215), resulting in a total of 48-80 differentially expressed bands, and that all of theses bands were isolated from the gel (p. 215).

Wadhwa *et al.* do not teach the use of such a method wherein the samples are taken from a part of the organism distant to the area of said disease.

Ditkoff *et al.* teach methods useful for detecting circulating thyroid cells in blood which comprise using RT-PCR on mRNA species taken from patients either known to have or suspected of metastatic thyroid cancer. The methods taught by Ditkoff *et al.* include

(a) isolating mRNA from a diseased patients, reverse transcribing the mRNA, amplifying the cDNA (p. 963-964);

(b) isolating mRNA from a normal volunteers, reverse transcribing the mRNA, amplifying the cDNA (p. 963-964);

(c) separating the cDNA species using gel electrophoresis and ethidium bromide label (p. 964).

Ditkoff *et al.* teach that thyroglobulin was expressed in the blood samples of patients with metastatic thyroid cancer and with thyroid cancer and no current metastases, but not in any of the patients with benign thyroid disease or the normal volunteers (ABSTRACT).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the methods for obtaining isolated selected mRNA species useful for diagnosing or identifying a disease as taught by Wadhwa *et al.* by sampling areas distant from the site of disease, such as blood, as taught by Ditkoff *et al.* in order to identify mRNA species useful for disease detection. The ordinary practitioner would have been motivated to combine these methods because Wadhwa *et al.* teach that "Differential display of mRNA species has recently been developed as a simple, sensitive, and powerful method to identify differentially expressed genes in in vitro and in vivo biological systems from different origins or under different conditions (p. 213)" and Ditkoff *et al.* exemplify that in fact the expression of certain mRNA species at an area distant from disease has important diagnostic value. The ordinary practitioner would have been motivated to combine these methods to provide a method for determining additional sequences with diagnostic utility.

4. Claims 18, 21-23, 25-26, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Graber *et al.* (Annals of Surgical Oncology, 3(2): 192-197) in view of Ditkoff *et al.* (Surgery, 120(6): 959-964, 1996).

Graber *et al.* teach a method of obtaining isolated selected cDNA species which comprising:

(a) isolating mRNA from a normal esophageal mucosa tissue sample, reverse transcribing the mRNA, and amplifying the cDNA (p. 193);

(b) isolating mRNA from a carcinoma of the esophagus sample, reverse transcribing the mRNA, and amplifying the cDNA (p. 193);

(c) separating the cDNA species using gel electrophoresis (p. 193)

(d) selecting two or more cDNA species from the separated cDNA species obtained in step (c), which are present at a different level in the normal sample than in the diseased sample (Fig. 1); and

(e) isolating the resulting selected cDNA species by excision from the gel (p. 194).

The tissue samples were human tissue obtained from The Cooperative Human Tissue Network of the National Disease Research Institute or from patients. With regard to claim 23, which requires that the cDNA is labeled, Graber *et al.* do not expressly teach this limitation, however, labeling of the cDNA is an inherent property of the autoradiography method that Graber *et al.* use to visualize the bands (p. 193, Fig. 1).

Graber *et al.* do not teach the use of such a method wherein the samples are taken from a part of the organism distant to the area of said disease.

Ditkoff *et al.* teach methods useful for detecting circulating thyroid cells in blood which comprise using RT-PCR on mRNA species taken from patients either known to have or suspected of metastatic thyroid cancer. The methods taught by Ditkoff *et al.* include

(a) isolating mRNA from a diseased patients, reverse transcribing the mRNA, amplifying the cDNA (p. 963-964);

(b) isolating mRNA from a normal volunteers, reverse transcribing the mRNA, amplifying the cDNA (p. 963-964);

(c) separating the cDNA species using gel electrophoresis and ethidium bromide label (p. 964).

Ditkoff *et al.* teach that thyroglobulin was expressed in the blood samples of patients with metastatic thyroid cancer and with thyroid cancer and no current metastases, but not in any of the patients with benign thyroid disease or the normal volunteers (ABSTRACT).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the methods for obtaining isolated selected mRNA species useful for diagnosing or identifying a disease as taught by Graber *et al.* by sampling areas distant from the site of disease, such as blood, as taught by Ditkoff *et al.* in order to identify mRNA species useful for disease detection. The ordinary practitioner would have been motivated to combine these methods because Graber *et al.* teach that "differential display can be used to isolate cDNAs of widely varying levels of expression (p. 196)," and they further teach that genes can be identified "without any prior knowledge of their sequence or function (p. 193), and Ditkoff *et al.* exemplify that in fact the expression of certain mRNA species at an area distant from disease has important diagnostic value. The ordinary practitioner would have been motivated to combine these methods to provide a method for determining additional sequences with diagnostic utility.

5. Claims 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wadhwa *et al.* in view Ditkoff *et al.* as applied to claims18-25 and 27 above, and further in view of the Stratagene Catalog (1988).

The teachings of Wadhwa *et al.* in view of Ditkoff *et al.* are applied herein as discussed above. It is especially noted that Wadhwa *et al.* teach methods in which labeled cDNA samples (both normal and transformed samples) are exposed to the immobilized cDNA species to produce a gene transcript pattern.

Wadhwa *et al.* in view of Ditkoff *et al.* do not teach the packaging of the immobilized cDNA species into a kit, nor do they teach this method as a method for making a kit.

Stratagene teaches gene characterization kits. The ordinary practitioner would have been motivated to used the method disclosed by Wadhwa *et al.* in view of Ditkoff *et al.* to produce a kit containing the cDNAs on a solid support and other reagents useful for gene transcript comparisons, such as the a normal and diseased samples as taught by Wadhwa *et al.* in view of Ditkoff *et al.* to be used in nucleic acid research since the Stratagene catalog expressly teaches the benefits to the practitioner of kits:

> "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, pre-mixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control."

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself and thus represents an intended use of the kit (see MPEP 2111.02). Therefore, the kits of the instant claims are *prima facie* obvious over the disclosure of Wadhwa *et al.* in view of Ditkoff *et al.*, further in view of the Stratagene catalog.

6. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wadhwa *et al.* in view of Ditkoff *et al.* in view of the Stratagene Catalog as applied to claims 29-34 above, and further in view of Seilhamer *et al.* (WO 95/20681).

The teachings of Wadhwa *et al.* in view of Ditkoff *et al.* in view of the Stratagene Catalog is applied to this claim as discussed above.

Wadhwa *et al.* in view of the Stratagene Catalog do not teach a method in which a test sample is compared to a known sample for diagnosis of a disease.

Seilhamer *et al.* teach that a gene transcripts from a biological specimen can be quantified and compared to against the transcripts of a diseased and healthy patients in order to diagnose a disease (p. 12, lines 5-20). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included such a comparison step in the methods taught by Wadhwa *et al.* in view of Ditkoff *et al.* in view of the Stratagene catalog in order to have provided a method for the diagnosis of disease since Seilhamer teach that such comparisons are useful for disease diagnosis.

RESPONSE TO REMARKS

Applicant's arguments are centered around the fact that neither Wadhwa *et al.* nor Graber *et al.* teach methods in which the sample from the diseased specimen is taken from a location distant from the point of the disease, a limitation which was added to the claims by amendment. These arguments are addressed by the addition of Ditkoff *et al.* to the rejections, as discussed above.

Conclusion

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C. Einsmann
Examiner
Art Unit 1655

February 12, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

2/12/01